Guidance for Industry

Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing

DRAFT GUIDANCE

This guidance is being distributed for internal comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 45 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Lizzie Sanchez, 301-827-5847.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2002

OGD

Guidance for Industry

Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing

Additional copies are available from:

Division of Drug Information HFD-240
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, Maryland 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2002

OGD

J:\!GUIDANC\4955dft.doc
07/31/02

TABLE OF CONTENTS

Guidance for Industry[1]

Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance is intended to provide information to sponsors of abbreviated new drug applications (ANDAs) on the design of bioequivalence studies for modified-release dosage forms of potassium chloride. A guidance on this topic was first issued May 15, 1987, and revised June 6, 1994. The May 1987 guidance recommended a single-dose, three-way crossover study. This revision provides recommendations for a two-way crossover design comparing the generic product to the reference listed drug (RLD). In addition, the use of analysis of covariance (ANCOVA), recommended in the original guidance, is no longer recommended. The Agency has determined that analysis of variance (ANOVA) with baseline correction is adequate for bioequivalence analysis of pharmacokinetic data obtained following oral administration of potassium chloride drug products. The in vitro dissolution testing and criteria for waivers of in vivo testing for lower strengths have also been revised to reflect the Agency thinking in the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*, issued in October 2000.

[1] This guidance has been prepared by the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

II. BACKGROUND

The potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance of normal renal function. The intracellular concentration of potassium is approximately 150 to 160 milliequivalents (mEq) per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent and under steady state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50 to 100 mEq per day.

Potassium supplements are indicated for the treatment of patients with potassium depletion (hypokalemia) with or without metabolic alkalosis and in digitalis intoxication in patients with hypokalemic familial periodic paralysis. It is also indicated for the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop (e.g., patients receiving digitalis therapy or patients with significant cardiac arrhythmias).

Urinary potassium measurements are commonly used in studies of bioavailability and bioequivalence. Because of the homeostatic mechanisms that maintain serum potassium levels within a relatively narrow range, serum levels do not necessarily reflect intake.

The most common adverse reactions to oral potassium chloride are nausea, vomiting, flatulence, abdominal pain and/or discomfort, and diarrhea. Patients should be instructed to take each dose with a full glass of water or other liquid.

III. IN VIVO STUDIES

A. Product Information

1. FDA Designated Reference Product

Potassium chloride for oral administration is marketed as various solid oral dosage forms. Applicants should consult FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book) for the desired product.

2. Batch Size

The test batch or lot should be manufactured under production conditions and should be of a size at least 10 percent that of the largest lot planned for production, or a minimum of 100,000 units, **whichever is larger.**

3. Potency

The assayed potency of the reference product should not differ from that of the test product by more than 5 percent.

B. Single-Dose Bioequivalence Study

1. Objective

The objective of a single-dose bioequivalence study should be to compare the rate and extent of absorption of a generic potassium chloride formulation with that of a reference formulation.

2. Methodology

The recommended study design is a two-treatment, two-period, two-sequence crossover. Each subject should receive a single oral dose of potassium chloride at 80 mEq of both the test and reference formulations. Extensive urine sampling for determination of urinary potassium excretion should be performed before and after each dose. Creatinine clearance should be determined to ensure that urine collection has been adequate.

3. Inclusion/Exclusion Criteria

The applicant should include a sufficient number of subjects in the study to demonstrate bioequivalence. Subjects eligible for participation should be between the ages of 20 and 40 years, within $\pm$ 10 percent of ideal body weight. Study subjects should be asked not to undertake vigorous physical exercise beginning 7 days prior to the start of the study period and continuing until discharge from the clinic. Alcoholic beverages should not be consumed for a period beginning 48 hours prior to drug administration and ending after study completion.

Subjects with any of the following conditions should be excluded from the study:

- Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, or adrenal-pituitary disorders, as evidenced by medical exam, physical exam, and/or clinical laboratory tests
- Use of tobacco in any form, currently or within the 6 months prior to study initiation
- Use of any known enzyme inducers or inhibitors within 30 days prior to study entry
- History of drug or alcohol abuse
- History of hypersensitivity to the drug or similar compounds
- Use of any prescription or nonprescription (OTC) medication within 2 weeks prior to study entry

- Pregnancy, nursing, or failure to use a medically acceptable form of contraception by female subjects

4. Dietary and Housing Considerations

The subjects should be placed on a standardized diet, with known amounts of potassium, sodium, calories, and fluid. Fluid intake should be maintained at 3,000 to 5,000 ml/day to ensure an adequate rate of urine flow throughout the study period. This is higher than the normal fluid intake of 1300 to 2500 ml/day. Strict control and knowledge of the actual intake of potassium, sodium, calories, and fluid are critical for study success.

Study subjects should be placed in a climate-controlled environment, remaining in-house as much as possible. Physical activity should be restricted to avoid excessive sweating and thus potassium loss. Detailed information regarding the composition of the diet should be included in the final report. Meals, snacks, and fluids should be given at standard times, and subjects should be strongly encouraged to ingest the recommended amounts and refrain from unnecessary physical activity. In addition, subjects should be queried regarding any prolonged episodes of diarrhea or excessive sweating, as these occurrences may invalidate or obscure the results. A test for fecal occult blood should be performed on each dosing day.

5. Collection of Urine and Blood Samples

The volume of each urine collection should be recorded. Aliquots of each urine collection should be stored frozen until assayed for potassium. After the aliquots are drawn, all remaining urine samples for each subject over a 24-hour period can be pooled for urine creatinine determination. A blood sample should be drawn at approximately the same time each day for serum creatinine determination.

6. Study Design

The study should be conducted over a single period of residence in the clinic, the duration of which is 16 days and 17 nights. This should be divided into two periods of 8 days, with dose administration to take place on days 7 and 15. Recommended study procedures are identical for each of the 8-day periods (see Appendix A). The schedule for study periods 1 and 2 follows.

Diet Equilibration Days, Days 1-4 and 9-12

- Diets should be standardized to provide the following daily intake of potassium, sodium, and calories:

  Potassium: 50-60 mEq
  Sodium: 160-180 mEq
  Calories: 2500-3500

- Fluids should be administered according to the following schedule:

500 ml of room temperature water initially (at 7:00 hours)
200 ml every hour afterwards for 12 hours
Additional (known) amounts of fluid can be administered at the investigator's discretion from 19:00 hours until 7:00 hours the following day.

- No urine is collected during the diet equilibration days.

Baseline Days, Days 5-6 and 13-14

- The standard diet and fluid schedule should continue as described for the equilibration days.

- Urine should be collected each day to establish each subject's baseline level of potassium excretion.

- Urine collection intervals should be at hours 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24.

- Urine collection should begin at 7:00 hours. On Days 5 and 13, subjects can dispose of this sample. On Days 6 and 14, the urine collected at 7:00 hours completes the 16-24 hour sample.

- Samples for creatinine clearance determination should be collected on Days 6 and 14.

Drug Dosing Days, Days 7 and 15

- After an 8-hour overnight fast, 80 mEq of either test or reference product should be given by mouth at 7:00 hours with 500 ml room temperature water.

- Subjects should remain upright (sitting upright, standing, or slowly walking) for at least 3 hours following dosing.

- The standard diet and fluid schedule should continue as described for the equilibration days.

- Urine collection times should be as on Days 6 and 14.

- Samples should be collected for creatinine clearance determination.

- Stool samples for determination of fecal occult blood should be collected any time from 8 hours post-dosing until the next bowel movement.

Post-Drug Dosing Days, Days 8 and 16

- The standard diet and fluid schedule should continue as described for the equilibration days.

- Urine collection times should be as on Days 7 and 15.

- Samples should be collected for creatinine clearance determination.

Discharge, Day 17

- Subjects can be discharged following the final urine collection at 7:00 hours.

7. Clinical Report and Adverse Reactions

Patient medical histories, physical examination reports, and all incidents of possible adverse reactions should be reported.

8. Retention of Samples

Retention samples of study drug products must be maintained (21 CFR 320.38), normally at the testing facility where the study was conducted. The study sponsor should provide the testing facility with a sufficient supply of the test and the reference products to complete the study and retain the appropriate number of dosage units as reserve samples. The study sponsor should not predetermine the samples to be retained prior to sending the batches to the testing facility. The testing facility will randomly select the reserve samples from the supply sent by the sponsor. This is to ensure that reserve samples are in fact representative of the same batches provided by the study sponsor for the testing. For more information on retention of bioequivalence samples, please refer to 21 CFR 320.38 and 320.63.

IV. DATA ANALYSIS

Baseline excretion of potassium (obtained during the baseline days) should be subtracted from the amount obtained on the drug dosing day to yield the net effect of drug administration. The baseline data used should be the average of the two readings obtained on the two baseline days and be subject specific and period specific (e.g., for subject #12, his **period II** amount of baseline excretion should **only** be used to adjust his **period II** drug dosing day amount). Although fluctuations in the baseline are expected, differences in baseline excretion amounts for the two baseline days should not differ by more than 100 percent.

The following information on urine potassium concentration data should be recorded for each subject:

- Amount excreted in each collection interval (Ae)
- Cumulative urinary excretion from 0-24 hours (Ae0-24h)
- Cumulative urinary excretion from 0-48 hours (Ae0-48h)

- Maximal rate of urinary excretion (Rmax)
- Time of maximal urinary excretion (Tmax)
- Area under the excretion rate vs. time curve ($AUCr = [\{R_1+R_2\}*\{t_2-t_1\}/2]$)
- Excretion rate in each collection interval (R)
- Midpoint of each collection interval (t)

All data should be calculated using baseline adjusted and non-baseline adjusted data. Statistical analysis ($p = 0.05$) should be done by ANOVA for baseline adjusted parameters, and the 90 percent confidence intervals generated for natural log-transformed and nontransformed cumulative urinary excretion from 0-24 (Ae_{0-24}) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure should be used to determine 90 percent confidence intervals.

V. IN VITRO TESTING

A. Dissolution Testing

Dissolution testing should be conducted on 12 individual dosage units from the batches of test and reference products used in the bioequivalence studies. Early sampling times of 1, 2, and 4 hours should be included in the sampling schedule to ensure against premature release of the drug (dose dumping) from the formulation. The recommended general dissolution conditions are shown below.

1. Apparatus	USP 24 Apparatus I (rotating basket) for capsules USP 24 Apparatus 2 (paddle) for tablets
2. Rotation Speed	100 rpm (basket) 50 rpm (paddle)
3. Temperature	37 □0.5°C
4. Units to Be Tested	12
5. Dissolution Medium	900 ml of de-ionized water
6. Sampling schedule	1, 2, 4 hours, and every 2 hours thereafter, until 80% of the drug is released.

Specifications for the dissolution procedure to ensure quality control will be determined on a case-by-case basis.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP 24.

VI. WAIVER OF IN VIVO TESTING FOR LOWER STRENGTHS

Waiver of in vivo bioequivalence study requirements for the lower strengths of a generic product can be granted (21 CFR 320.22(d)(2)) provided the following conditions are met.

- The in vivo study on the highest strength is acceptable and demonstrates that the test potassium chloride product is bioequivalent to the corresponding reference product.

- The lower strengths are proportionally similar in both active and inactive ingredients to the strengths tested in vivo, and have the same drug release mechanism.

- All strengths meet an appropriate in vitro dissolution test. Dissolution profiles between the highest strength and the lower strengths should be similar, based on the f2 test using the method described previously (V.A) and in three additional dissolution media (e.g., pH 1.2, 4.5, and 6.8).

Appendix A: STUDY SCHEDULE

Bioequivalence Study Schedule for Potassium Chloride ER Tablets, Capsules																		
Activity	Day	Days								Days								
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Admit to Clinic	X																	
Diet Equilibration		X	X	X	X					X	X	X	X					
Baseline						X	X							X	X			
Drug Dosing								X								X		
Post-Drug Dosing									X								X	
Collect Urine Samples						X	X	X	X					X	X	X	X	
24 –hr Creatinine Clearance							X	X	X						X	X	X	
Fecal Occult Blood								X								X		
Discharge																		X

REFERENCES

Physicians' Desk Reference, 55th Edition, 2001.

Schuirmann, D.J., "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability," *J Pharmacokinet Biopharm*, 1987; 15:657-80.

Skelly, J.P., G.L. Amidon, W.K. Barr, et al., "Workshop Report: In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms," *Pharm Res,* 1990; 7:975-82.

Food and Drug Administration, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, October 2000.